Detailed monitoring of the effects of mannitol following experimental head injury

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The experimental model of a cerebral missile injury developed by Crockard was used in three groups of Rhesus monkeys treated with mannitol. One group received mannitol 15 minutes after being injured with a BB pellet at 90 m/sec impact. Another group was wounded identically, but mannitol treatment was delayed until 1 hour after injury. The last group was wounded with the missile traveling at 180 m/sec, and mannitol was started 15 minutes after trauma. The data were contrasted with the results from the original model. After receiving mannitol, all groups showed marked improvement in mean blood pressure, cerebral perfusion pressure, cerebral blood flow, and cerebral metabolic rate of oxygen consumption out of proportion to the degree of reduction in intracranial pressure (ICP). The authors conclude that the therapeutic value of mannitol may, in some injuries, be directly related to its effects on blood flow and metabolism, as well as to its better known effects upon ICP.

KEY WORDS  •  head injury  •  cerebral blood flow  •  cerebral metabolism  •  intracranial pressure  •  cardiac output  •  mannitol

Numerous clinical studies have been conducted on the physiological consequences of head injury at various intervals after trauma. However, the data concerning the first few hours after injury are scarce. In recent articles by Crockard, et al., an experimental cerebral missile injury model is described in the Rhesus monkey. The physiological consequences of the injury have been recorded in detail for the initial 6-hour period. The results include a rapid, profound rise in intracranial pressure (ICP), and a significant reduction in hemispheric cerebral blood flow (CBF), which was attributed to a reduction in cardiac output. The injury was so severe that 45% of the animals receiving the standard missile injury (velocity of 90 m/sec) had died within 6 hours. A recent study by Obrist, et al., who found reduced flow fairly consistently in serial measurements after severe head injury in humans, adds support to the validity of the model of the injured Rhesus monkey.

The current paper deals with the effects of mannitol on the physiological consequences of the bullet injury in an attempt to answer several questions. Is the primary injury so severe that it is not an appropriate model to fairly assess various treatment modalities? Does the injury so disrupt the blood-brain barrier that mannitol cannot reduce ICP? Even if mannitol were effective in the standard injury, could it be effective in a high-velocity (180 m/sec) missile injury? Finally, if treatment is effective, can it be delayed?

Materials and Methods

Twenty-eight adult Rhesus monkeys (Macaca mulatta), weighing 5 to 9 kg, were used in the mannitol-treatment group. Their data were compared with 30 untreated animals: 21 were from our initial experiments, and nine were added to the standard-injury group to obtain values for cardiac output, viscosity, and systemic blood volume (SBV). Of the 21 of the original untreated animals, 14 received a standard injury, and the other seven received a high-velocity injury. The experimental preparation has been described in detail previously.

The animals were tranquilized with phencyclidine hydrochloride, 1 to 2 mg/kg intramuscularly, repeated as required. A small dose of barbiturate, 2 mg/kg intravenously, was occasionally required also, but none was given within 1 hour before the injury. A cuffed endotracheal tube was placed. A catheter was inserted into the femoral artery to monitor mean arterial blood pressure (MABP) and heart rate, and to sample for osmolality, hematocrit, lactate, viscosity, and blood gases. A Swan Ganz catheter was inserted via the femoral vein to monitor pulmonary wedge
pressure (PWP) and cardiac output by thermodilution. Fluids were delivered through a catheter in the opposite femoral vein. Chromium-51-tagged red cells were injected to determine SBV at baseline and 2 hours after injury. Respirations were recorded with a pneumograph, and temperature was maintained at 38° to 39° C with a heating pad. The animals were held in a stereotaxic frame.

Epidural balloons were placed through biparietal burr holes to monitor ICP. A 3-mm hole was made over the confluens sinuum to obtain cerebral venous blood gases; except during sampling this hole was occluded with bone wax. A 7-mm hole was made in the right occipital area 10 mm above the nuchal line, and 12 mm to the right of the midline. A 310-gm BB gun was fired through this hole on a line 5° divergent from midline. The bullet typically came to rest at the upper outer quadrant of the right orbit. This path was chosen to avoid direct damage to the brain stem and major blood vessels. A No. 22 needle was inserted percutaneously into the lumbar subarachnoid space to obtain ½-ml samples of cerebrospinal fluid (CSF) for osmolality testing.

For CBF determinations, xenon-133 was injected directly into the common carotid artery after ligation of the external carotid branches and placement of a single focused collimator over each hemisphere. The CBF was calculated by the initial slope technique. Since pCO2 changes were insignificant, we felt that correcting flow to a standard pCO2 was unjustified. Oxygen content, arterial-venous oxygen difference (A-V O2 difference), cerebral metabolic rate of oxygen consumption (CMRO2), cerebral perfusion pressure (CPP), and cerebral vascular resistance (CVR) were calculated as previously described. Means, standard error of means (SEM), and t-tests were calculated in a conventional fashion.

Following control observations, a missile with predetermined velocity was fired through the right cerebral hemisphere with a Crossman 160 air rifle, which was attached to a stereotaxic frame. The burr hole was then sealed with methyl methacrylate. All observations were repeated at 1, 10, and 30 minutes following injury, and then hourly until death or at 6 hours.

The animals treated with mannitol were divided into three groups. Group 1 (13 animals) received a standard velocity injury (90 m/sec or 5.02 joules), and started receiving treatment at 15 minutes following trauma. Group 2 (eight animals) also received a standard injury, but mannitol was withheld until 1 hour following trauma. Group 3 (seven animals) received a high-velocity injury (180 m/sec or 5.02 joules), and mannitol was initiated 15 minutes after injury. The mannitol was given as a 25% solution in joules), and mannitol was initiated 15 minutes after injury. The CBF fell from a control of 42.6 to 16 ml/100 gm/min in the untreated animals at 30 minutes. This value was significantly improved after mannitol to 33.5 ml/100 gm/min (p < 0.001) by 30 minutes.

Results

None of the animals had a significant epidural, subdural, or intracerebral hematoma. The following results are listed as the group mean ± SEM for each time interval. Note that the animals that were not treated are referred to as the “untreated” group, not as the “control” group. “Control” refers to baseline observations before the gunshot wound.

Group 1

These seven animals were wounded with a missile traveling 90 m/sec, and started receiving treatment at 15 minutes. Immediately after impact, a reduction in respiratory rate and an increase in tidal volume were seen. The pattern returned to control levels within a few minutes, and was unaffected by mannitol. No significant changes in arterial blood gases were observed. The heart rate showed an initial bradycardia after injury but had returned to normal within 30 minutes, and was unaffected by the mannitol given at 15 minutes.

The MABP rose initially and then began to fall at 15 minutes as it had for the untreated group. With the untreated group, the MABP continued to fall progressively with time. However, treatment with mannitol at 15 minutes reversed this hypotensive trend (Fig. 1), so that by 2 hours after injury there was a significant difference between the MABP of the untreated (79 mm Hg) and the treated group (89 ± 5.6 mm Hg; p < 0.02). At the end of 6 hours, the difference was marked: 55 mm Hg in the untreated and 86 ± 5.1 mm Hg in the treated group (p < 0.01). The latter MABP is not significantly different from that obtained during the control period (p > 0.4).

The ICP rose immediately at 1 minute to 59 ± 7.1 mm Hg, and fell to 49 ± 3.2 mm Hg by 10 minutes. Treatment with mannitol at 15 minutes increased the rate of decline (Fig. 2). At 30 minutes, ICP was 18 ± 2.1 mm Hg, contrasted to 36 mm Hg in the untreated group (p < 0.05). The ICP at 1 hour was also significantly different from that of the untreated group, but during the 2- to 6-hour period the difference was not significant. A mean of 4.9 boluses of mannitol, 0.5 gm/kg each bolus, was required for the group.

Cerebral perfusion pressure fell to nearly half of control values immediately following injury (45.3 ± 5.6 mm Hg). Following administration of mannitol at 15 minutes, CPP rose to 71 ± 4.8 mm Hg at 30 minutes and remained near this level through 6 hours (Fig. 3). This value is significantly higher than the untreated value of 55 mm Hg at 30 minutes (p < 0.05), but the CPP remained significantly lower than control values (92 mm Hg) throughout the entire 6-hour period.

The CBF fell from a control of 42.6 to 16 ml/100 gm/min in the untreated animals at 30 minutes. This value was significantly improved after mannitol to 33.5 ml/100 gm/min (p < 0.001) by 30 minutes.

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Fig. 1. The changes in mean arterial blood pressure in untreated and mannitol-treated animals after cerebral gunshot wound (GSW).

following injury. The difference remained significant at each time interval, and steady improvement of flow occurred so that the CBF at 6 hours (39.4 ml/100 gm/min) had virtually returned to control values (Fig. 4). All of the flow changes were virtually identical for the right (injured) and left (uninjured) hemispheres, even though direct wounding was limited to the right.

The net effect of mannitol was to stabilize the CVR. In the untreated animals the CVR decreased from 2.2 to 1.86 peripheral resistance units (PRU) over the first 10 minutes, then rose significantly at 30 minutes to 2.75 PRU, and remained elevated through 3 hours. From 4 to 6 hours it fell significantly to 0.76 PRU. After mannitol, the CVR was 2.15 ± 0.11 PRU, and barely changed during the remainder of the experiment (Fig. 5) for the group given mannitol.

The CMRO₂ showed a steady decline from 3.12 to 1.51 ml/100 gm/min at 30 minutes in the untreated group. However, with treatment at 15 minutes, the CMRO₂ (2.18 ml/100 gm/min) was significantly higher than the untreated group at 30 minutes (p < 0.02). The CMRO₂ continued to improve toward normal, and by 6 hours the value was 2.76 ± 0.20 ml/100 gm/min (Fig. 6). However, the A-V O₂ differences followed the same pattern as in the untreated group (Fig. 7).

Six of the seven animals (86%) treated at 15 minutes survived until sacrifice at 6 hours. The other lived for 5 hours. This result compares favorably to the 55% 6-hour survival rate in the untreated animals.

An additional six animals were treated with mannitol as above, and in these additional measurements of SBV, blood viscosity, and cardiac output were performed. Before injury and 2 hours after trauma (1⅓ hours following initiation of mannitol) SBV was measured. The mean control value was 263.5 ± 2.0 ml, and after mannitol it was 259 ± 4.4 ml. The viscosity of the arterial blood in the untreated animals remained fairly constant throughout the early part of the experiment, but at 6 hours it rose to 140% of baseline. The viscosity of the mannitol group began to decline after the first bolus and reached a value of only 30% of baseline as early as 2 hours after injury (Fig. 8). Finally, one of the most dramatic effects of mannitol was on cardiac output. In the untreated animals, cardiac output was only 0.53 liters/min at 30 minutes, whereas in the mannitol group it was 1.08 liters/min, measured at the same time interval (Fig. 9).
Group 2

A group of eight animals received a gunshot wound with a velocity of 90 m/sec. Mannitol treatment was withheld until 1 hour after injury. The data of the first hour following injury will not be discussed because they closely resemble those of the untreated animals. The data from 2 to 6 hours after injury will be compared to the untreated group, as well as to the group treated at 15 minutes.

Heart rate, respiratory pattern, and blood gases were not affected by mannitol treatment at 1 hour. The MABP remained significantly higher than that of the untreated group for the entire 2- to 6-hour period (p < 0.05). It promptly improved to the same level as that of the group treated 15 minutes following injury (Fig. 1).

The pattern of ICP reduction did not significantly differ from the rate of decline of the untreated animals, despite the fact that a mean of 4.1 boluses of mannitol were used. At 2 hours following injury the ICP of Group 2 animals remained significantly higher than that of Group 1 (Fig. 2).

The CPP was significantly higher than that of the untreated group at 4 and 6 hours. The pattern of CPP was virtually the same as that of Group 1 during the 2- to 6-hour period (Fig. 3).

The CBF improved following mannitol and was significantly higher than that of the untreated animals for the 2- to 6-hour period (p < 0.02). It paralleled the improvement of the 15-minute treatment group (Group 1) but remained slightly lower at each interval (Fig. 4). The CBF at 6 hours (34.6 ± 1.3 ml/100 gm/min) did not differ significantly from control values.

The CVR was significantly higher than the untreated animals at 4 and 6 hours (p < 0.02), and was barely different from control baseline values from 2 to 6 hours. It showed the same pattern as that in animals treated with mannitol at 15 minutes (Fig. 5).

The CMRO₂ improved significantly over that of the untreated animals during the 2- to 6-hour period (p < 0.01), but not as significantly as that of the 15-minute treatment group (Group 1). At 6 hours the Group 2 animals had a CMRO₂ of 2.10 ± 0.20 ml/100 gm/min, which contrasted significantly to 2.76 ± 2.0 ml/100 gm/min in Group 1 (p < 0.05) (Fig. 6). Again, the A-V O₂ differences showed a similar pattern for the two groups (Fig. 7.).
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FIG. 3. The changes in cerebral perfusion pressure in untreated and mannitol-treated animals after cerebral gunshot wound (GSW).

FIG. 4. The changes in cerebral blood flow in untreated and mannitol-treated animals after cerebral gunshot wound (GSW).

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FIG. 5. The changes in cerebral vascular resistance in untreated and mannitol-treated animals after cerebral gunshot wound (GSW).

FIG. 6. The changes in cerebral metabolic rate of oxygen consumption in untreated and mannitol-treated animals after cerebral gunshot wound.
Fig. 7. The changes in arterial-venous oxygen content difference in untreated and mannitol-treated animals after cerebral gunshot wound.

Fig. 8. The changes in cardiac output in untreated animals (circles) and animals treated with mannitol at 15 minutes after cerebral gunshot wound (squares).
One treated animal died at 1 hour, and another at 4½ hours. The remaining six were alive at 6 hours (75% survivors). Three of these were allowed to awaken from anesthesia. Two of these survived with a left hemiparesis and normal conscious level; the other was lethargic at 2 days and was sacrificed because of inability to care for himself.

Blood and CSF osmolalities before and after mannitol were compared in a group consisting of four animals from Group I and four animals from Group 2. The values were virtually identical at control: 293 ± 2.5 mOsm/liter for blood and 295 ± 3.5 mOsm/liter for CSF. After mannitol, both blood and CSF osmolalities rose, but blood levels were significantly higher (p < 0.05) than CSF levels at all intervals tested (Fig. 10). The gradient between blood and CSF ranged from 5 to 8 mOsm/liter. At the end of 6 hours, the serum osmolality was 318 ± 0.9 mOsm/liter.

**Group 3**

These seven animals were wounded with a missile traveling at 180 m/sec. Treatment was initiated as with the first group at 15 minutes. A 1-hour treatment group was not used since none of the untreated animals lived more than 1 hour. Since only three of the seven treated animals lived more than 1 hour, no statistical tests other than means were used in the following observations.

There was a period of apnea immediately following injury in five of the animals. This period ranged from 20 seconds to 4 minutes. None of the animals was given ventilatory support.

Immediately after injury there was a profound bradycardia with the heart rate falling to 50% of control. Treatment was started at 15 minutes, and by 30 minutes the heart rate had continued to increase to over 90% of control. The upward trend continued so that the heart rate was 115% of control from 3 to 6 hours following injury.

At 1 minute after injury the MABP increased to 180% of control but by 10 minutes had fallen to 83% of control. The MABP remained at this level for the untreated animals, but by 1 hour the MABP of the treated animals had recovered to 113% of control. A gradual downward trend then ensued so that at 6 hours the MABP in the treated group was at 80% of control (Fig. 1).

The ICP results are quite different between the untreated and the mannitol groups. Both had a rapid pressure elevation to about 75 mm Hg at 1 minute, but at 10 minutes the former was 24 mm Hg; the latter, 50 mm Hg. The disparity may be due to the fact that the data from only three animals were used in the former group (animals requiring ventilatory support were not included) compared to seven in the latter. By 2 hours, the ICP was reduced to the levels seen in the standard-injury group that was treated at 15 minutes (Group 1) (Fig. 2). A mean of 4.2 ± 1.3 boluses of mannitol were given to the four animals that survived long enough to be treated.

In the untreated animals, the CPP fell to 55% of control by 10 minutes and remained near this level throughout the first hour. After treatment with mannitol, the CPP rose to 75% of control and stabilized at this level. This response was very similar to that of the standard-injury group after treatment at 15 minutes (Fig. 3).
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In the untreated animals, the CBF first increased and then fell to very low values (29% of control). However, in the animals treated with mannitol at 15 minutes, the CBF recovered to 82% of control at 30 minutes and remained near this level. This compares favorably to the value of 76% which was obtained at 30 minutes for Group 1 animals (Fig. 4).

The CVR initially fell and then rose to very high levels (170% of control at 30 minutes) in the untreated animals. The effect of mannitol at 15 minutes was to halt the elevation of CVR so that the values obtained from 30 minutes to 6 hours were near control values (Fig. 5).

The pattern seen in CMRO₂ paralleled that of CBF. In the untreated animals CMRO₂ was 234% of control at 1 minute but had fallen to 65% of control by 30 minutes. The effect of mannitol was to halt the reduction, so that the CMRO₂ at 30 minutes was 122% of control. At subsequent intervals the CMRO₂ hovered near control values (Fig. 6). Again, mannitol treatment had no significant effect on A-V O₂ differences (Fig. 7).

Three of the animals died within 15 minutes of injury. One died at 45 minutes. One died at 5½ hours. The remaining two survived the full 6 hours (29% survivors). None of the untreated animals survived past 1 hour.

Discussion

Mannitol has long been accepted as a reliable agent in the reduction of raised ICP from both traumatic and nontraumatic causes. It can reduce ICP by 26% or more within 5 minutes of administration. The reduction of ICP depends on the establishment of an osmotic gradient between brain and blood by mannitol. The fact that mannitol, when given early, significantly reduced the ICP in our animals suggests that some integrity of the blood-brain barrier is maintained. Although serum and CSF osmolalities rise simultaneously, which suggests a leakage of mannitol across the blood-brain barrier, a clear gradient between serum and CSF is established and maintained after the initiation of mannitol therapy. Normally, at serum osmolalities of higher than 310 mOsm/liter, the blood-brain barrier to mannitol is disrupted; however, the CSF levels tend to rise more slowly than the serum levels. In our animals, however, the CSF and serum levels rose at similar rates. Therefore, it could be concluded that the effect of the missile injury was to alter but not destroy the normal blood-brain barrier.

Although mannitol did reduce the ICP, it had a more striking influence on some of the other parameters, such as MABP, CPP, CBF, and CMRO₂. The only statistically significant reductions in ICP were at 30 minutes and 1 hour for the Group 1 animals. At 2 hours there was still a significant difference between the ICP of the standard-injury group treated at 15 minutes (Group 1) and that treated at 1 hour (Group 2). However, there was no longer any significant difference between the two groups for any of the other parameters at this point. Therefore, the mannitol seemed to have a beneficial effect on the other parameters that could not be explained as simply the result of ICP reduction alone. It has already been shown in uninjured animals that mannitol will produce an increase in CBF without altering ICP.

In the untreated animals, brain-stem signs were striking soon after injury. Hypertension, bradycardia, and apnea were seen and were the most profound in the group receiving the high-energy missile injury. Following the systemic hypertension, hypotension ensued. Thus, the associated reduction in cardiac output may represent myocardial depression as an effect of brain-stem injury. Since raised ICP was not of lasting significance in this model, the reduced cardiac output appears to play a major role in the depressed cerebral blood flow and metabolism. These findings may accompany closed head injuries as well, for Nilsson, et al., demonstrated systemic hypotension following an 11-m/sec acceleration injury in the rat. Indeed, trauma per se in the form of a thermal injury has been associated with systemic hypotension before loss of body fluid.

One of the most striking effects of mannitol was to return the cardiac output to nearly normal values shortly after its administration. Improvement in MABP, CPP, CBF, and CMRO₂ followed. The improvement may in part be related to a positive inotropic effect of mannitol or through some beneficial effect on the brain stem, such as reversing brain-stem oligemia. The improvement in cardiac function was not simply related to an increase in SBV through mannitol, for we have shown that mannitol did not significantly alter the systemic blood volume at 2 hours.

The improvement in CBF may also be related to lowered blood viscosity. Although the CBF eventually returned to normal values, the CPP remained significantly below normal. Thus, the lowered blood viscosity may have helped restore normal flow through lowering vascular resistance enough to compensate for the reduced CPP.

As seen above, treatment may be effective in the high-velocity injury, as well as in the standard injury, with very early initiation of therapy. With the standard injury, treatment may be delayed but the quality of survival (as speculated from the CMRO₂) may be affected. Mannitol treatment is effective even though the blood-brain barrier is not entirely intact. Treatment not only improves the rate of survival, but also the various parameters investigated are much closer to normal in those that are treated than those that survive without treatment.

When ICP is monitored in the clinical head-injury setting, mannitol is usually given only when ICP is elevated. As we have observed, the untreated animals do not appear to die from raised ICP, but the MABP, CPP, CBF, CMRO₂, and cardiac output are quite
low. Therefore, in view of the findings of improvement in blood flow and brain metabolism when mannitol is given, apparently mediated through improved cardiac function and lowered blood viscosity, the clinician might wish to give mannitol in the early stages of a severe head injury in order to improve overall function rather than wait for a rise in ICP before initiating therapy.

References


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